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Effects of antihypertensive treatment on endpoints in the diabetic patients randomized in the Systolic Hypertension in Europe (Syst-Eur) trial

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ABSTRACT: In this review we attempt to determine the role of calcium channel blockers in preventing cardiovascular sequela in patients with both hypertension and diabetes mellitus. The data have been collected from three sources: *post hoc* analyses of subgroups of diabetic patients in placebo-controlled hypertension trials (SHEP, Syst-Eur, Syst-China); a stepped care blood pressure oriented trial (HOT); and comparative trials primarily focussing on metabolic aspects and intermediate endpoints (ABCD, FACET).

On balance, the data seem to indicate that long-acting calcium channel blockers score remarkably well in preventing cardiovascular complications in diabetic hypertensive patients.

Key words: *Hypertension, Diabetes, Prospective antihypertensive trials, Trial endpoints, Dihydropiridine-type long-acting calcium channel blockers, ACE-inhibitors*

INTRODUCTION

Hypertension and diabetes are widely recognized as mutually reinforcing factors leading to premature cardiovascular complications and renal disease (1). The present review is intended to highlight the potential of blood pressure control in the prevention of cardiovascular sequela in diabetic patients with hypertension. Whenever possible, the efficacy of long-acting calcium channel blockers has been compared either with placebo or with other antihypertensive drugs. The vast majority of patients under consideration had type 2 diabetes and were under appropriate conventional antidiabetic control.

OVERVIEW OF TRIALS

The main hypertension trials which have included diabetic patients are listed in Table I. A major contribution in this area has been made by the Systolic Hypertension in the Elderly Program (SHEP). In this trial (2,3), most cardiovascular events were reduced to a similar degree by chlorthalidone-based treatment (vs. placebo) in diabetic and non-diabetic hypertensive patients. It is noteworthy that coronary events were reduced even more in diabetic than in non-diabetic patients. This overall outcome turned out to be more favourable than might have been expected on the basis of the rather negative metabolic profile, including insulin resistance, of thiazide-type diuretics (4).

More recently, a similar *post-hoc* subgroup analysis has been performed in the study population of the Systolic Hypertension in Europe (Syst-Eur) trial (5,6). In that trial, 492 (10.5%) of 4695 randomized patients with isolated systolic hypertension had diabetes (5). The latter had on average a 1.7 mm Hg higher systolic blood pressure and a 1.1 mm Hg lower diastolic blood pressure than the non-diabetic patients. Treatment steps in the double-blind Syst-Eur trial were: nitrendipine (10-40 mg/day), enalapril (5-20 mg/day) and hydrochlorothiazide (12.5-25 mg/day) titrated or combined to reduce systolic pressure by 20 mm Hg to below 150 mm Hg; in the control group matching placebo tablets were used similarly. After a median follow-up of 2 years, blood pressure corrected for placebo effects, was reduced to a similar extent in diabetics and nondiabetics (systolic/diastolic pressure: -8.6/-3.9

mm Hg and -10.3/-4.6 mm Hg, respectively). Nevertheless, the benefits in preventing endpoints were considerably greater in diabetic than in nondiabetic patients, as indicated in Table II. Furthermore, the benefit conferred by active treatment was similar in the patient who remained on monotherapy with nitrendipine to those who progressed to combined therapy (7).

The SHEP (2,3) and Syst-Eur (5,6) trials were remarkably similar in design and size, with only one principal difference, i.e., the choice of the first-line antihypertensive drug: chlorthalidone and nitrendipine, respectively. We thus decided to compare the results obtained in these two trials. As shown in Table III the validity of such a comparison is sustained by the similar net decreases in blood pressure, similar risks in the placebo groups regardless of the absence or presence of diabetes, and the identity of relative outcome benefits of active treatment in the nondiabetics. The only major difference occurred in the actively treated diabetic subgroups, where three major events declined 2-4 times as much on treatment with a calcium channel blocker as on treatment with a thiazide (SHEP). Our conclusion is therefore at variance with the recom-

TABLE I - TRIALS REPORTING OUTCOME IN DIABETIC PATIENTS WITH HYPERTENSION

Trial (references)	Diabetics No. (%)*	Main study drugs
Placebo-controlled		
SHEP (2,3)	590 (12.3)	chlorthalidone † vs. placebo
Syst-Eur (5,6)	492 (10.5)	nitrendipine † vs. placebo
Syst-China (8)	98 (4.1)	nitrendipine † vs. placebo
Other designs		
ABCD (19)	470 (100)‡	nisoldipine vs. enalapril †
FACET (20)	380 (100)	amlodipine vs. fosinopril †
HOT (17,18)	1501 (8.0)	felodipine to reach diastolic pressure ≤ 90 mm Hg † vs. ≤ 80 mm Hg

**Number of diabetics (percentage of total number of patients enrolled)*
† Identifies the treatment on which outcome was significantly better in diabetic patients with hypertension
‡ Results in 480 normotensive diabetic patients not reported.

TABLE II - BENEFIT OF ANTIHYPERTENSIVE TREATMENT IN DIABETIC AND NON-DIABETIC PATIENTS RANDOMIZED IN THE SYST-EUR TRIAL

Nature of end point	Diabetics				Nondiabetics			
	Placebo* (N=240)	Active treatment* (N=252)	Change (%) †	P‡	Placebo* (N=2057)	Active treatment* (N=2146)	Change (%) †	P‡
Mortality								
total	45.1 (26)	26.4(16)	-41 (-69,9)	0.09	21.6 (111)	19.8 (107)	-8 (-30, 20)	0.55
cardiovascular	27.8 (16)	8.3 (5)	-70 (-89, -19)	0.01	11.9 (61)	10.0 (54)	-16 (-42, 22)	0.37
Fatal and non fatal end points								
all cardiovascular	57.6 (31)	22.0 (13)	-62 (-80, -19)	0.002	31.4 (155)	23.5 (124)	-25 (-41, -5)	0.02
stroke	26.6 (15)	8.3 (5)	-69 (-89, -14)	0.02	12.3 (62)	7.8 (42)	-36 (-57, -5)	0.02
cardiac end points	27.1 (15)	1.17 (7)	-57 (-82, 6)	0.06	19.7 (99)	15.4 (82)	-22 (-42, 5)	0.10

** End points per 1000 patient-years (number of events).*
† Change with active treatment with 95% confidence interval between parentheses.
‡ Significance for the comparison between placebo and active treatment.

mendation by the SHEP investigators to prescribe low-dose diuretics as the first step of antihypertensive treatment in diabetic patients with hypertension (3). On the contrary, we would rather advise using nitrendipine-like calcium channel blockers as first choice, in view of the event-free survival and vascular protection observed in the Syst-Eur trial (5).

In the placebo-controlled Systolic Hypertension in China (Syst-China) trial (8), the first line active medication was also nitrendipine (10-40 mg/day), to which captopril (12.5-50 mg/day) and/or hydrochlorothiazide (12.5-50 mglday) could be added to control blood pressure. In the placebo group diabetes raised the risk of all endpoints 2-3 times ($P \leq 0.05$). However, active treatment reduced the excess risk associated with diabetes to a nonsignificant level except for cardiovascular mortality. Thus, in line with the Syst-Eur findings (5,6), the Chinese trial showed that treatment starting with a dihydropyridine calcium channel blocker was particularly beneficial in older diabetic patients with systolic hypertension (8).

The mechanisms underlying the particular benefit of calcium channel blockers are a matter of speculation; they may well be multiple. A major role may be attributable to the absence of metabolic side effects from calcium channel blockers, such as glucose intolerance and perturbations of the serum lipid profile (9,10), to which thiazide-treated diabetic patients seem to be particularly vulnerable (11). In addition, calcium channel blockers may provide renal protection (12,13) and exert beneficial effects on the rheology of the blood (14) and on endothelial function (15,16). The relevance of these hypothetic mechanisms remains open to further investigation.

The Hypertension Optimal Treatment (HOT) Study (17,18) produced confirmatory evidence on a positive interaction between calcium channel blockade and the presence of diabetes in older hypertensive patients. In this trial (Tab. I) no less than 18790 hypertensive patients from 26 countries (mean age 61.5 years) were randomized to reach one of 3 target levels of diastolic blood pressure (90, 85 or 80 mm Hg). The calcium channel blocker felodipine served as the mainstay of treatment (5-10 mg/day), with the potential addition of angiotensin converting enzyme inhibitors or beta-blockers. The actual blood pressure levels attained in the three groups turned out to be closer than expected: 143.7/85.2 mm Hg, 141.4/83.2 mm Hg and 139.7/81.1 mm Hg, respectively. Table IV shows the effects of randomization to a target diastolic blood pressure of 90 and 80 mm Hg, respectively. With the exception of a greater incidence of myocardial infarctions in the subpopulation randomized to 90 mm Hg compared with the one targeted to 80 mm Hg,

TABLE III - RESULTS OF THE SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM (SHEP) AND THE SYSTOLIC HYPERTENSION IN EUROPE TRIAL (SYST-EUR) IN DIABETIC AND NON-DIABETIC PATIENTS

	Diabetics		Nondiabetics	
	SHEP*	Syst-Eur*	SHEP*	Syst-Eur*
N (%)	590 (12.3)	492 (10.5)	4149 (87.7)	4203 (89.5)
Mean blood pressure reduction †				
systolic (mm Hg)	-9.8	-8.6	-12.5	-10.3
diastolic (mm Hg)	-2.2	-3.9	-4.1	-4.6
Risk in placebo group ‡				
total mortality	35.6	45.1	21.8	21.6
cardiovascular end points	63.0	55.0	36.8	28.9
stroke	28.8	26.6	15.0	12.3
coronary events	32.2	23.1	15.2	12.4
Change with active treatment (%) §				
mortality	-26 (-54, 18)	-64 (-83, -25)	-15 (-32, 6)	-18 (-40,13)
all cardiovascular end points	-34 (-54, -6)	-68 (-84, -35)	-34 (-45, -21)	30 (-47, -8)
stroke	-22 (-55, 34)	-86 (-96, -58)	-38 (-54, -17)	-39 (-60, -7)
coronary events	-56 (-75, -23)	-58 (-87, 37)	-19 (-38, 5)	-22 (-47, 17)

** In the SHEP trial (2,3) active treatment consisted of chlorthalidine (12.5-25 mg/day) with the possible addition of atenolol (25-50 mg/day) or reserpine (0.05-0.1 mg/day); in the Syst-Eur trial (5,6) active treatment consisted of nitrendipine (10-40 mg/day) with the possible addition of enalapril (5-20 mg/day) and/or hydrochlorothiazide (12.5-25 mg/day). † The mean effect of active treatment on blood pressure was corrected for baseline and placebo. ‡ Rate expressed as events per 1000 patient-years. §The changes with active treatment were calculated by Cox regression with adjustments applied for sex, age, smoking, systolic and diastolic blood pressure at baseline, electrocardiographic abnormalities (SHEP) or previous cardiovascular complications (Syst-Eur) at baseline, and race (SHEP) or residence in western Europe (Syst-Eur).*

there were in the study population as a whole no differences in outcome. By contrast, the diabetic patients (8%) randomized to a goal diastolic blood pressure of 80 mm Hg fared significantly better than those assigned to attaining a diastolic blood pressure of 90 mm Hg. In fact, the risk of fatal and nonfatal cardiovascular events was 2 to 3 times higher in the latter group. This substantial impact of a rather modest reduction in the achieved diastolic blood pressure (-4.1 mm Hg) may come as a surprise. However, in the Syst-Eur diabetic subgroup (5), similar differences in endpoint rates have been observed (Tab. II) in the face of equally modest net reductions in diastolic blood pressure (6).

These mutually corroborating results obtained independently in two large randomized prospective trials of different design are ostensibly at variance with the results of some earlier studies (19,20). The Appropriate Blood Pressure Control in Diabetes (ABCD) trial was originally designed to compare progression of diabetic nephropathy under treatment with the angiotensin converting enzyme inhibitor enalapril or with the calcium channel blocker nisoldipine. Hypertensive patients (N=470) were randomized to either active enalapril (5-40 mg per day) plus nisoldipine placebo or to active nisoldipine (10-60 mg per day) plus enalapril placebo tablets, all administered in a double-blind manner. After 87 months of study, the Data and Safety Monitoring Committee observed a statistically significant difference in the rates of cardiovascular events between the two groups (i.e., a preponderance of myocardial infarctions in the nisoldipine group) and hence recommended stopping the double-blind regimen. This decision to prematurely stop the trial is open to criticism. Myocardial infarction was not a prespecified endpoint. Treatment status at the time of the myocardial infarctions was not reported. This is important because premature discontinuation of the double-blind study medication and the addition of beta-blockers and thiazides to the study drugs may well have been in favor of the enalapril group. No first-ever event analysis has been made available. All of these deficiencies may have enhanced the chance of a biased finding.

The Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) was an open-label randomized study in patients with hypertension and type 2 diabetes (20). Its primary purpose was to assess treatment-related differences in diabetes control, serum lipids and renal function. The patients were randomly assigned to receive fosinopril (20 mg/day) or amlodipine (10 mg/day) as the first-line antihypertensive drug. If blood pressure remained uncontrolled, the alternative drug was added to the initial regimen. According to intention-to-treat analysis, patients receiving fosinopril as first-line drug appeared to have significantly lower risk of the combined outcomes of acute myocardial infarction, stroke, or hospitalization for angina than those receiving amlodipine (14/189 vs. 27/191 events).

The interpretation of the above results is handicapped by a number of confounding factors. First of all, 58 patients randomized to fosinopril (30.7%) and 50 from the amlodipine group (26.2%) ended up receiving the combination of both drugs, which makes any sensible interpretation rather precarious. An even more serious objection arises from the fact that microalbuminuria at entry was significantly higher in the amlodipine group (24 ± 1 μg/min) than in the fosinopril group (20 ± 1 μg/min; $P<0.05$). A difference in this order of magnitude may well have been a crucial determinant of the uneven outcome, since in type 2 diabetic patients, the extent of microalbuminuria is at least as accurate in predicting cardiovascular morbidity and mortality as that of cholesterol levels, hypertension, smoking, and even pre-existing coronary artery disease (21-23).

Although the FACET authors recognize the fact that their trial was unsuited to detecting a difference in vascular events between the two treatment

TABLE IV - RELATIVE RISKS IN THE HYPERTENSION OPTIMAL TREATMENT TRIAL* (19,20) IN PATIENTS RANDOMIZED TO A TARGET DIASTOLIC BLOOD PRESSURE OF 90 VS. 80 mmHG

	All patients	Diabetics only
Number of patients randomized		
to 90 mm Hg	6264	501
to 80 mm Hg	6262	499
Relative risk†		
total mortality	0.91 (0.74-1.10)	1.77 (0.98-3.21)°
cardiovascular mortality	0.90 (0.68-1.21)	3.00 (1.28-7.08)ª
major cardiovascular events	1.07 (0.89-1.28)	2.06 (1.24 3.44)ᵇ
myocardial infarction	1.37 (0 99-1.91)ª	2.01 (0.81-4.97)
stroke	1.05 (0.79-1 .41)	1.43 (0.68-2.99)

** Felodipine (5-10 mg/day), unless contra-indicated, was the first-line antihypertensive treatment in all patients*

† 95% confidence interval presented between parentheses. o indicates P=0.07; a, P≤0.05; and b, p≤0.01

groups (20), they nevertheless maintain their preference for angiotensin converting enzyme inhibitors versus calcium channel blockers as first-line treatment of diabetic hypertensive patients.

Conclusion

One difficulty in assessing the merits or hazards of calcium channel blockers vs. other drug classes in diabetic hypertensive patients is that the latter have often been recruited as subgroups in larger trials in hypertension. This situation has necessarily turned the evaluation of the treatment effects in the diabetic subgroups into a *post-hoc* exercise. In our view, this handicap is a limited one which has been largely compensated for by the strict adherence in the statistical analyses to predetermined unadulterated endpoints. In this regard, the parent trials such as SHEP (2,3), Syst-Eur (5,6), Syst-China (8) and HOT (17,18) appear to have distinguished themselves as compared to the "adaptive" trials which deviated from their original design (19,20) in midstream. The evidence in favor of using dihydropiridine-type long-acting calcium channel blockers, exemplified above by nitrendipine and felodipine, as first-line antihypertensive treatment in diabetic hypertensive patients seems to be overwhelming, both in quantitative and qualitative terms when considering cardiovascular outcome.

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